Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, gonadotropin, or clomiphene for unexplained infertility. N Engl J Med 2015;373:1230-40. DOI: 10.1056/NEJMoa1414827

Table of Contents

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Table S1. Baseline characteristics of the women-per protocol analysis*

Variable	Gonadotropin (N=249)	Clomiphene (N=251)	Letrozole (N=246)
Biometric features			
Age-yr	32.3± 4.0	32.1±4.4	32.1±4.1
Body mass index (kg/m2) †	26.6±6.6	26.8±6.5	27.3±6.4
Race/Ethnicity-no. (%) ‡			
White	198 (79.5)	209 (83.3)	209 (85.0)
Black	16 (6.4)	23 (9.2)	18 (7.3)
Asian	25 (10.0)	12 (4.8)	8 (3.3)
Mixed race	7 (2.8)	4 (1.6)	8 (3.3)
Hispanic or Latino	26 (10.4)	24 (9.6)	27 (11.0)
Fertility history			
Length of time attempting conception-mo	34.1± 25.4	32.9±22.9	34.4±26.1
Previous Live birth-no. (%)	53 (21.3)	60 (23.9)	37 (15.0)
Ultrasonographic findings			
Antral follicle count-both ovaries	20.2± 11.6	20.3±11.3	21.3±10.8
Endometrial thickness sagittal plane-mm	6.7±3.2	7.0±3.1	6.8±3.1
Fasting serum biochemical values			
Total testosterone-ng/dL	26.6±31.9	24.7±17.2	25.4±16.4

SHBG-nmol/L	59.0±27.3	59.7±29.6	60.5±28.4
Estradiol-pg/mL	34.3±43.8	31.8±20.6	31.3±15.1
Progesterone-ng/mL	0.8±0.8	0.8±0.4	0.8±0.6
AMH-ng/mL	2.5±1.9	2.7±2.2	2.7±2.0
TSH-uIU/mL	2.0±1.0	2.0±1.0	1.9±1.0
Prolactin-ng/mL	11.9±7.5	11.0±6.1	11.4±7.7
LH-mIU/mL	4.9±2.5	5.0±2.5	5.4±3.4
FSH-mIU/mL	6.9±2.2	7.0±2.0	6.9±2.2
DHEAS-ug/dL	133.6±62.7	129.2±66.7	131.8±67.1

*Plus‐minus values are means ±SD. Expect for previous live birth (p=0.04), there were no significant differences (P<0.05) among the three groups in any other baseline characteristics.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race or ethnic group was reported by the patients. Some patients chose more than one category, including Hispanic or Latino.

Table S2. Reasons for cycle cancellation in different treatment groups

Reasons for cycle cancellation	**Gonadotropin Group**	**Clomiphene Group**	**Letrozole Group**	**Total**
1. Leading follicle does not reach a mean diameter of 18 mm after 18 days of treatment	3	4	12	19
2. Endogenous LH surge happens with a mean diameter of the leading follicle <16 mm	5	4	10	19
3. Increased risk for OHSS and/or high-order multiple gestational pregnancy exists when more than 4 growing follicles develop (mean diameter >18 mm)	16	5	0	21
4. The serum E2 exceeds 3000 pg/m around the day of expected hCG administration	11	0	0	11
5. Patient or partner related reasons (withdrawal, unable to complete the cycle, no show, patient request, family reasons, etc.	12	14	3	29
6. Already ovulated	3	2	3	8
7. Others (Physician discretion, irregularly shaped follicle, fluctuating E2 levels, patient pregnant, etc.)	8	1	7	16
Total	**58**	**30**	**35**	**123**

Table S3. Time to conception, clinical pregnancy among patients who conceived, and pregnancy loss*

Variable	Gonadotropin group (N=301)	Clomiphene group (N=300)	Letrozole group (N=299)	Gonadotropin + Clomiphene group (N=601)	Absolute difference between clomiphene and gonadotropin	Absolute difference between Letrozole and gonadotropin	Absolute difference between clomiphene and Letrozole	Absolute difference between (gonadotropin + clomiphene) and Letrozole
	no./total no. (%)				% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Conception †	140/301(46.5)	106/300(35.3)	85/299(28.4)	246/601(40.9)	-11.2 (-19.0 to -3.4) ¶	-18.1 (-25.7 to -10.5) ‖	6.9(-0.5 to 14.4)	12.5(6.1 to 19.0) ‖
Time to conception-days ‡	62.3 ±43.8	67.4 ±49.8	67.2 ±55.6	64.6 ±46.4	5.1(-7.2 to 17.2)	4.8(-9.6 to 19.2)	0.3(-15.2 to 15.8)	-2.6(-16.3 to 11.1)
Clinical Pregnancy among patients who conceived	107/140(76.4)	85/106(80.2)	67/85(78.8)	192/246(78.1)	3.8(-6.6 to 14.1)	2.4(-8.8 to 13.6)	1.4(-10.2 to 12.9)	-0.8(-10.9 to 9.3)
Singleton pregnancy	73/140(52.1)	77/106(72.6)	58/85(68.2)	150/246(61.0)	20.5(8.7 to 32.4) ‖	16.1(3.2 to 29.0)	4.4(-8.6 to 17.4)	-7.3(-18.9 to 4.4)
Multiple pregnancy	34/140(24.3)	8/106(7.6)	9/85(10.6)	42/246(17.1)	-16.7(-25.4 to -8.0) ‖	-13.7(-23.4 to -4.0)	-3.0(-11.3 to 5.2)	6.5(-1.6 to 14.5)
Twin pregnancy	24/140(17.1)	8/106(7.6)	9/85(10.6)	32/246(13.0)	-9.6(-17.6 to -1.6)	-6.6(-15.6 to 2.5)	-3.0(-11.3 to 5.2)	2.4(-5.4 to 10.2)
Triplet pregnancy	10/140(7.1)	0	0	10/246(4.1)	-7.1(-11.4 to -2.9) ¶	-7.1(-11.4 to -2.9)	0	4.1(-0.9 to 7.6)
Gestations with one or more losses	51/140(36.4)	31/106(29.2)	26/85(30.6)	82/246(33.3)	-7.2(-19.9 to 4.6)	-5.8(-18.5 to 6.8)	-1.3(-14.4 to 11.7)	2.8(-8.7 to 14.2)
Loss in first trimester	48/140(34.3)	28/106(26.4)	25/85(29.4)	76/246(30.9)	-7.9(-19.4 to 3.6)	-4.9(-17.4 to 7.6)	-3.0(-15.8 to 9.8)	1.5(-9.8 to 12.8)
Biochemical factor or no fetal heart motion	23/140(16.4)	14/106(13.2)	13/85(15.3)	37/246(15.0)	-3.2(-12.1 to 5.6)	-1.1(-10.9 to 8.7)	-2.1(-12.1 to 7.9)	-0.3(-9.1 to 8.6)
Ectopic pregnancy	11/140(7.9)	5/106(4.7)	5/85(5.9)	16/246(6.5)	-3.1(-9.2 to 2.9)	-2.0(-8.7 to 4.7)	-1.2(-7.6 to 5.3)	0.6(-5.3 to 6.5)
Treated pregnancy of unknown location	1/140(0.7)	2/106(1.9)	0	3/246(1.2)	1.2(-1.8 to 4.1)	-0.7(-2.1 to 0.7)	1.9(-0.7 to 4.5)	1.2(-0.2 to 2.6)
Loss after observed heart motion	13/140(9.3)	7/106(6.6)	7/85(8.2)	20/246(8.1)	-2.7(-9.4 to 4.1)	-1.1(-8.6 to 6.5)	-1.6(-9.2 to 5.9)	-0.1(-6.9 to 6.7)
Loss in second or third trimester	3/140(2.1)	3/106(2.8)	1/85(1.2)	6/246(2.4)	0.7(-3.3 to 4.7)	-1.0(-4.3 to 2.4)	1.7(-2.3 to 5.6)	1.3(-1.7 to 4.3)

*Conception was defined as having a rising serum level of human chorionic gonadotropin for two consecutive tests, Clinical pregnancy was defined as an intrauterine pregnancy with fetal heart motion, as determined by transvaginal ultrasonography.

† Two gestations known to have conceived were lost to follow up before determination of clinical pregnancy were excluded, 1 in gonadotropin group, 1 in clomiphene group.

‡ Days between the first day the subjects took medicine and the first day of positive pregnancy test recorded.

¶ P<0.01.

‖ P<0.001.

Table S4. Live birth, multiple live birth, clinical pregnancy, multiple clinical pregnancy, and conception rates per cycle*

Variable	Gonadotropin group (N=301)	Clomiphene group (N=300)	Letrozole group (N=299)	Absolute difference between clomiphene and gonadotropin	Absolute difference between letrozole and gonadotropin	Absolute difference clomiphene and letrozole
		no./total no. (%)		% (95% CI)	% (95% CI)	% (95% CI)
Live birth per treatment cycle						
Pre- treatment cycle 1	1/301(0.3)	0/300(0)	0/299(0)	-0.3(-1.0 to 0.3)	-0.3(-1.0 to 0.3)	0
Treatment cycle 1	47/292(16.1)	31/294(10.5)	25/288(8.7)	-5.6(-11.0 to -0.1)	-7.4(-12.7 to -2.1) †	1.9(-2.9 to 6.7)
Treatment cycle 2	23/217(10.6)	15/235(6.4)	10/242(4.1)	-4.2(-9.4 to 0.9)	-6.5(-11.3 to -1.7) †	2.3(-1.8 to 6.3)
Treatment cycle 3	19/160(11.9)	11/195(5.6)	10/204(4.9)	-6.2(-12.2 to -0.3)	-7.0(-12.8 to -1.2)	0.7(-3.7 to 5.1)
Treatment cycle 4	7/110(6.4)	13/163(8.0)	11/172(6.4)	-0.4(-6.3 to 5.4)	0.0(-5.9 to 5.8)	1.6(-4.0 to 7.1)
Multiple live birth per treatment cycle						
Pre- treatment cycle 1	0/301(0.0%)	0/300(0.0%)	0/299(0.0%)			
Treatment cycle 1	10/292(3.4%)	3/294(1.0%)	3/288(1.0%)	-2.4(-4.8 to -0.0)	-2.4(-4.8 to 0.0)	-0.0(-1.7 to 1.6)
Treatment cycle 2	10/217(4.6%)	0/235(0.0%)	1/242(0.4%)	-4.6(-7.4 to -1.8) ‡	-4.2(-7.1 to -1.3) †	-0.4(-1.2 to 0.4)
Treatment cycle 3	8/160(5.0%)	0/195(0.0%)	3/204(1.5%)	-5.0(-8.4 to -1.6) †	-3.5(-7.3 to 0.2)	-1.5(-3.1 to 0.2)
Treatment cycle 4	3/110(2.7%)	1/163(0.6%)	1/172(0.6%)	-2.1(-5.4 to 1.2)	-2.1(-5.4 to 1.1)	0.0(-1.6 to 1.7)
Clinical pregnancy per treatment cycle						
Pre- treatment cycle 1	1/301(0.3)	0/300(0)	1/299(0.3)	-0.3(-1.0 to 0.3)	0.0(-0.9 to 0.9)	-0.3(-1.0 to 0.3)
Treatment cycle 1	50/292(17.1)	38/294(12.9)	28/288(9.7)	-4.2(-10.0 to 1.6)	-7.4(-12.9 to -1.9) †	3.2(-1.9 to 8.3)
Treatment cycle 2	26/217(12.0)	18/235(7.7)	13/242(5.4)	-4.3(-9.8 to 1.2)	-6.6(-11.8 to -1.4)	2.3(-2.1 to 6.7)
Treatment cycle 3	23/160(14.4)	13/195(6.7)	13/204(6.4)	-7.7(-14.2 to -1.2)	-8.0(-14.4 to -1.6)	0.3(-4.6 to 5.1)
Treatment cycle 4	7/110(6.4)	16/163(9.8)	12/172(7.0)	3.5(-3.0 to 9.9)	0.6(-5.3 to 6.6)	2.8(-3.3 to 8.8)
Multiple clinical pregnancy per treatment cycle						

Pre- treatment cycle 1	0/301(0.0%)	0/300(0.0%)	0/299(0.0%)			
Treatment cycle 1	11/292(3.8%)	5/294(1.7%)	3/288(1.0%)	-2.1(-4.7 to 0.6)	-2.7(-5.2 to -0.2)	0.7(-1.2 to 2.5)
Treatment cycle 2	12/217(5.5%)	1/235(0.4%)	2/242(0.8%)	-5.1(-8.3 to -2.0) ‡	-4.7(-8.0 to -1.5) †	-0.4(-1.8 to 1.0)
Treatment cycle 3	8/160(5.0%)	1/195(0.5%)	3/204(1.5%)	-4.5(-8.0 to -1.0)	-3.5(-7.3 to 0.2)	-1.0(-2.9 to 1.0)
Treatment cycle 4	3/110(2.7%)	1/163(0.6%)	1/172(0.6%)	-2.1(-5.4 to 1.2)	-2.1(-5.4 to 1.1)	0.0(-1.6 to 1.7)
Conception per treatment cycle						
Pre- treatment cycle 1	2/301(0.7)	0/300(0)	2/299(0.7)	-0.7(-1.6 to 0.3)	0.0(-1.3 to 1.3)	-0.7(-1.6 to 0.3)
Treatment cycle 1	63/292(21.6)	47/294(16.0)	39/288(13.5)	-5.6(-11.9 to 0.7)	-8.0(-14.2 to -1.9)	2.4(-3.3 to 8.2)
Treatment cycle 2	37/217(17.1)	25/235(10.6)	19/242(7.9)	-6.4(-12.8 to -0.04)	-9.2(-15.2 to -3.2) †	2.8(-2.4 to 8.0)
Treatment cycle 3	30/160(18.8)	16/195(8.2)	13/204(6.4)	-10.5(-17.7 to -3.4) †	-12.4(-19.3 to -5.5) ‡	1.8(-3.3 to 6.9)
Treatment cycle 4	9/110(8.2)	19/163(11.7)	12/172(7.0)	3.5(-3.6 to 10.6)	-1.2(-7.6 to 5.2)	4.7(-1.6 to 10.9)

*Conception was defined as having a rising serum level of human chorionic gonadotropin for two consecutive tests. Clinical pregnancy was defined as an intrauterine pregnancy with fetal heart motion, as determined by transvaginal ultrasonography. Live birth was defined as the delivery of a viable infant. Chi-square or Fisher's exact test was used for statistical analysis.

†P<0.01.

‡P<0.001.

Table S5. Rates of conception, clinical pregnancy, live birth, and pregnancy loss-Per protocol analysis*

Variable	Gonadotropin group (N=249)	Clomiphene group (N=251)	Letrozole group (N=246)	Gonadotropin + Clomiphene group (N=500)	Absolute difference between clomiphene and gonadotropin	Absolute difference between letrozole and gonadotropin	Absolute difference between clomiphene and letrozole	Absolute difference between (gonadotropin + clomiphene) and letrozole
	no./total no. (%)				% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Conception†	140/249(56.2%)	106/251(42.2%)	85/246(34.6%)	246/500(49.2%)	-14.0(-22.7 to -5.3)¶	-21.7(-30.2 to -13.1)‖	7.7(-0.8 to 16.2)	14.6(7.3 to 22.0)‖
Time to conception (days)	62.3±43.8(131)	67.4±49.8(101)	67.2±55.6(80)	64.6±46.4(232)	5.1(-7.0 to 17.2)	4.8(-8.8 to 18.4)	0.3(-15.2 to 15.8)	-2.6(-15.1 to 9.9)
Clinical pregnancy among patients enrolled	107/249(43.0%)	85/251(33.9%)	67/246(27.2%)	192/500(38.4%)	-9.1(-17.6 to -0.6)	-15.7(-24.0 to -7.4)‖	6.6(-1.4 to 14.7)	11.2(4.2 to 18.2)¶
Clinical pregnancy among patients who conceived	107/140(76.4%)	85/106(80.2%)	67/85(78.8%)	192/246(78.0%)	3.8(-6.6 to 14.1)	2.4(-8.8 to 13.6)	1.4(-10.2 to 12.9)	-0.8(-10.9 to 9.3)
Singleton pregnancy	73/140(52.1%)	77/106(72.6%)	58/85(68.2%)	150/246(61.0%)	20.5(8.6 to 32.4)‖	16.1(3.2 to 29.0)	4.4(-8.6 to 17.4)	-7.3(-18.9 to 4.4)
Multiple pregnancy	34/140(24.3%)	8/106(7.5%)	9/85(10.6%)	42/246(17.1%)	-16.7(-25.4 to -8.0)‖	-13.7(-23.4 to -4.0)	-3.0(-11.3 to 5.2)	6.5(-1.6 to 14.5)
Twin pregnancy	24/140(17.1%)	8/106(7.5%)	9/85(10.6%)	32/246(13.0%)	-9.6(-17.6 to -1.6)	-6.6(-15.6 to 2.5)	-3.0(-11.3 to 5.2)	2.4(-5.4 to 10.2)
Triplet pregnancy	10/140(7.1%)	0/106(0.0%)	0/85(0.0%)	10/246(4.1%)	-7.1(-11.4 to -2.9)¶	-7.1(-11.4 to -2.9)	0	4.1(1.6 to 6.5)
Multiple clinical pregnancy among total clinical pregnancy	34/107(31.8%)	8/85(9.4%)	9/67(13.4%)	42/192(21.9%)	-22.4(-33.2 to -11.6)‖	-18.3(-30.4 to -6.3)¶	-4.0(-14.3 to 6.2)	8.4(-1.6 to 18.5)
Live birth‡	97/249(39.0%)	70/251(27.9%)	56/246(22.8%)	167/500(33.4%)	-11.1(-19.3 to -2.9)¶	-16.2(-24.2 to -8.2)‖	5.1(-2.5 to 12.8)	10.6(4.0 to 17.3)¶
Singleton live birth	66/249(26.5%)	66/251(26.3%)	48/246(19.5%)	132/500(26.4%)	-0.2(-7.9 to 7.5)	-7.0(-14.4 to 0.4)	6.8(-0.6 to 14.1)	6.9(0.6 to 13.2)
Twin live birth	25/249(10.0%)	4/251(1.6%)	8/246(3.3%)	29/500(5.8%)	-8.4(-12.5 to -4.4)‖	-6.8(-11.1 to -2.4)¶	-1.7(-4.4 to 1.0)	2.5(-0.5 to 5.6)
Triplet live birth	6/249(2.4%)	0/251(0.0%)	0/246(0.0%)	6/500(1.2%)	-2.4(-4.3 to -0.5)	-2.4(-4.3 to -0.5)	0	1.2(0.2 to 2.2)
Multiple gestations among total live birth§	31/97(32.0%)	4/70(5.7%)	8/56(14.3%)	35/167(21.0%)	-26.2(-37.0 to -15.5)‖	-17.7(-30.7 to -4.6)	-8.6(-19.2 to 2.1)	6.7(-4.4 to 17.7)
Gestations with one or more losses	51/140(36.4%)	31/106(29.2%)	26/85(30.6%)	82/246(33.3%)	-7.2(-19.0 to 4.6)	-5.8(-18.5 to 6.8)	-1.3(-14.4 to 11.7)	2.7(-8.7 to 14.2)
Loss in first trimester	48/140(34.3%)	28/106(26.4%)	25/85(29.4%)	76/246(30.9%)	-7.9(-19.4 to 3.6)	-4.9(-17.3 to 7.6)	-3.0(-15.8 to 9.8)	1.5(-9.8 to 12.8)
Biochemical factor or no fetal heart motion	23/140(16.4%)	14/106(13.2%)	13/85(15.3%)	37/246(15.0%)	-3.2(-12.1 to 5.7)	-1.1(-10.9 to 8.7)	-2.1(-12.1 to 7.9)	-0.3(-9.1 to 8.6)
Ectopic pregnancy	11/140(7.9%)	5/106(4.7%)	5/85(5.9%)	16/246(6.5%)	-3.1(-9.2 to 2.9)	-2.0(-8.7 to 4.7)	-1.2(-7.6 to 5.3)	0.6(-5.3 to 6.5)
Treated pregnancy of unknown location	1/140(0.7%)	2/106(1.9%)	0/85(0.0%)	3/246(1.2%)	1.2(-1.8 to 4.1)	-0.7(-2.1 to 0.7)	1.9(-0.7 to 4.5)	1.2(-0.2 to 2.6)
Loss after observed heart motion	13/140(9.3%)	7/106(6.6%)	7/85(8.2%)	20/246(8.1%)	-2.7(-9.4 to 4.1)	-1.1(-8.6 to 6.5)	-1.6(-9.1 to 5.9)	-0.1(-6.9 to 6.7)
Loss in second or third trimester	3/140(2.1%)	3/106(2.8%)	1/85(1.2%)	6/246(2.4%)	0.7(-3.3 to 4.7)	-1.0(-4.3 to 2.4)	1.7(-2.2 to 5.6)	1.3(-1.7 to 4.3)

*Conception was defined as having a rising serum level of human chorionic gonadotropin for two consecutive tests. Clinical pregnancy was defined as an intrauterine pregnancy with fetal heart motion, as determined by transvaginal ultrasonography. Live birth was defined as the delivery of a viable infant.

† Two gestations know to have conceived were lost to follow up before determination of clinical pregnancy were excluded, 1 in gonadotropin group, 1 in clomiphene group.

‡ Ten patients with clinical pregnancy were excluded because they were lost to follow up prior to delivery, 1 in gonadotropin group, 6 in clomiphene group, and 3 in letrozole group.

§ Number of deliveries with multiple babies divided by the number of women who have live births.

¶ P<0.01.

‖ P<0.001.

Table S6. Congenital anomaly

Case number	Treatment group	Brief description of congenital anomaly
1	Clomiphene	Aortic arch hypoplasia
2	Clomiphene	Congenital hypothyroidism
3	Clomiphene	Renal duplicated right collecting system and ureterocele
4	Letrozole	Hypospadias
5	Letrozole	Right facial hemangioma; Biventricular hypertrophy; Bifid uvula; Small cataracts bilaterally; Widening of the corneal horizontal diameter
6	Gonadatropin	Right club foot
7	Gonadatropin	Transposition of genes on chromosome 19*
8	Gonadatropin	Multiple VSDs
9	Gonadatropin	Twin A VSD Twin B VSD

*Pregnancy loss at 16 weeks, not included in Table 4.
VSD = Ventricular Septal Defect

Table S7. Neonatal complications by ovulation induction agent and number of fetuses.

	Gonadotropin				Clomiphene Citrate			Letrozole		
	Singleton	**Twin**	**Triplet**	**Total**	**Singleton**	**Twin**	**Total**	**Singleton**	**Twin**	**Total**
Neonatal complications	15*	11	4	30	12	1	13	12	3	15
Congenital malformations	1	2†	0	3	3	0	3	2	0	2
Hypoglycemia	0	0	0	0	0	0	0	0	0	0
Intracranial hemorrhage	0	0	0	0	1	0	1	0	0	0
Intrauterine growth restriction	3	3	1	7	2	0	2	0	1	1
Jaundice	9	8‡	3‡	20	8	1	9	9	2	11
Neonatal hospitalization >3 days	3	6	4	13	5§	0	5	4	3	7
Patent ductus	0	0	0	0	0	0	0	0	0	0
Respiratory distress	1	5¶	2¶	8	3	0	3	3	2	5

*One fetus may have more than one complications.

†Represents number of twin deliveries, one set of twins both had congenital malformations; in another set, only one neonate had congenital malformation.

‡Represents number of twin or triplet delivers, for which both twins (except two in gonadotropin group) or all triplets had jaundice.

§Including two neonatal hospitalization due to congenital anomaly: one is heart defect and preterm birth; another one is congenital hypothyroidism.

¶Represents number of twin or triplet delivers, for which both twins (except one in gonadotropin group) or all triplets (except one) had respiratory distress.

Table S8. Serious Adverse Events (all) and Adverse Events (with more than 2% of patients experiencing them) among treatment groups

Event	**Gonadotropin group**	**Clomiphene Group**	**Letrozole Group**	**P value for comparison among three groups***
		number (percent)		
Before conception in female subjects who received a study drug (N = 886)				
Total number of subjects	297	298	291	
Serious adverse event				
Presumed Pyelonephritis	1(0.3)	0	0	0.66
Pyosalpinx Post-IUI	1(0.3)	0	0	0.66
Other adverse event				
Abdominal bloating	81(27.3)	50(16.8)	54(18.6)	0.003
Abdominal/pelvic pain	114(38.4)	91(30.5)	105(36.1)	0.12
Acne	10(3.4)	11(3.7)	8(2.7)	0.81
Agitation	13(4.4)	23(7.7)	23(7.9)	0.15
Anxiety	6(2.0)	4(1.3)	2(0.7)	0.39
Back pain	28(9.4)	32(10.7)	29(10)	0.87
Blurred vision	0	9(3.0)	4(1.4)	0.003
Breast pain	65(21.9)	19(6.4)	21(7.2)	<0.001
Constipation	6(2.0)	28(9.4)	8(2.7)	<0.001
Depression	3(1.0)	7(2.3)	3(1.0)	0.39
Diarrhea	12(4.0)	11(3.7)	20(6.9)	0.15
Dizziness	17(5.7)	21(7.0)	19(6.5)	0.80
Dysmenorrhea	39(13.1)	31(10.4)	48(16.5)	0.09

Dyspepsia	29(9.8)	25(8.4)	32(11.0)	0.56
Extrapyramidal disorder	1(0.3)	4(1.3)	6(2.1)	0.15
Fatigue	56(18.9)	42(14.1)	46(15.8)	0.28
Flu like symptoms	4(1.3)	3(1.0)	9(3.1)	0.15
Headache	89(30.0)	104(34.9)	122(41.9)	0.01
Hot flashes	25(8.4)	92(30.9)	49(16.8)	<0.001
Injection site reaction	32(10.8)	6(2.0)	9(3.1)	<0.001
Insomnia	8(2.7)	17(5.7)	8(2.7)	0.09
Irritability	20(6.7)	21(7)	18(6.2)	0.91
Joint/limb pain	5(1.7)	8(2.7)	17(5.8)	0.02
Myalgia	4(1.3)	7(2.3)	4(1.4)	0.68
Nasopharyngitis	6(2.0)	5(1.7)	5(1.7)	0.94
Nausea	50(16.8)	42(14.1)	49(16.8)	0.57
Pain	1(0.3)	6(2)	4(1.4)	0.18
Vomiting	1(0.3)	4(1.3)	7(2.4)	0.08
After conception in female subjects who discontinued study drug (N = 329)				
Total number of subjects	139	107	83	
Serious adverse event - mother				
First trimester				
Cholecystitis	1(0.7)	0	0	1.00
Ectopic Pregnancy	11(7.9)	5(4.7)	5(6.0)	0.58
Ovarian Hyperstimulation Syndrome	1(0.7)	0	0	1.00
Pain due to ovarian enlargement	1(0.7)	0	0	1.00
Pregnancy of Unknown Location	1(0.7)	2(1.9)	0	0.48

Second and third trimester				
Acute viral illness	1(0.7)	0	0	1.00
Hemorrhagic Hematoma	0	0	1(1.2)	0.25
Hospitalization†	1(0.7)	0	0	1.00
Hyperemesis	2(1.4)	0	0	0.51
Hypertension	0	1(0.9)	1(1.2)	0.33
Severe Pre-eclampsia; HELLP syndrome hospitalization; preterm labor	0	1(0.9)	0	0.58
Delivery and postpartum				
Emergency C-Section due to eclampsia	1(0.7)	0	0	1.00
Hospitalization‡	0	0	1(1.2)	0.25
Other adverse event - mother				
First trimester				
Abdominal/pelvic pain	4(2.9)	2(1.9)	3(3.6)	0.84
Breast pain	0	0	5(6.0)	0.001
Nausea	3(2.2)	1(0.9)	0	0.47
Hospitalization during first trimester	0	2(1.9)	0	0.17
Second and third trimester				
Gestational diabetes	7(5.0)	6(5.6)	9(10.8)	0.21
Pre-eclampsia/eclampsia	13(9.4)	5(4.7)	6(7.2)	0.38
Pre-term labor	15(10.8)	4(3.7)	6(7.2)	0.12
Premature rupture of membrane	6(4.3)	1(0.9)	3(3.6)	0.3
Hyperemesis	8(5.8)	3(2.8)	2(2.4)	0.45
Incompetent cervix	1(0.7)	0	1(1.2)	0.72
Placental abnormalities§	10(7.2)	8(7.5)	5(6.0)	0.92

Other complication during pregnancy¶	7(5.0)	9(8.4)	3(3.6)	0.35
Delivery and postpartum				
Post-partum depression	4(2.9)	2(1.9)	1(1.2)	0.80
Post-partum hemorrhage	5(3.6)	1(0.9)	0	0.15
Post-partum infection	4(2.9)	3(2.8)	2(2.4)	1.00
Other post-partum complication ‖	3(2.2)	4(3.7)	3(3.6)	0.72
After 20 weeks pregnancy in fetus through neonatal period in infant (N =222)				
Total number of subjects	96	70	56	
Serious adverse event - fetus/infant				
Congenital anomaly**	3(3.1)	3(4.3)	2(3.6)	0.90
Neonatal death	0	0	1(1.8)	0.25
Other adverse event - fetus/infant				
Intrauterine growth restriction	7(7.3)	2(2.9)	1(1.8)	0.32
Neonatal hospitalization >3 days	13(13.5)	3(4.3)	7(12.5)	0.11
Neonatal infection	1(1.0)	0	0	1.00
Neonatal jaundice	19(19.8)	9(12.9)	11(19.6)	0.46
Neonatal respiratory distress syndrome	8(8.3)	3(4.3)	5(8.9)	0.57
Other complication of infant after delivery††	2(2.1)	6(8.6)	2(3.6)	0.15

*Chi-square or Fisher's exact test was used.

†Patient admitted to the hospital at 34 weeks gestation for lower abdominal, pelvic, and vaginal pain and a second admission for management of severe groin pain.

‡ Patient presented to the ER one week post uncomplicated C-section delivery with shortness of breath at rest and then was admitted to the hospital and worked up for pulmonary edema.

§Details see Supplemental Table 9.

¶For clomiphene these included 1) gestational HTN, no meds, 2) subchorionic bleed at 8weeks, 3) gestational HTN, 4) Maternal GBS, 5) Oligohydremia. dx @ 37 weeks, 6) Pregnancy Induced Hypertension, 7)elevated pressures in 3rd trimester, 8)1st trimester bleeding, 9)benign lesion of groin. For letrozole these included 1) Asthma exacerbation, 2) Polyhydramnios, 3) Pregnancy induced Hypertension. For gonadotropin these included 1) Polyhydramnios, 2) Gestational HTN, fractured/sprained 2 ribs, 3) Subchoronic hematoma dx at 10 weeks resolved at 12 weeks, 4) Cholecystitis at 36.5 wks, 5) MTHFR, 6) Urinary retention requiring in office catheterization, 7) Pregnancy induced hypertension.

‖ For clomiphene these included 1) Urinary Retention; Secondary Laceration of the Perineum, 2) HTN postpartum required Magnesium Sulfate, 3) Hematoma, 4) Bladder was nicked during c-section. For letrozle these included 1) Prolapsed bladder, 2) High blood pressure, 3) Pregnancy Induced Hypertension. For gonadotropin these included 1) Vaginal hematoma, 2) Blood pressure continue to rise after delivery so subject was given IV mag sulfate, 3) Back pain due to epidural.

** Details see Supplemental Table 6.

††For clomiphene these included 1) Tongue tied-frenulum cut, 2) Breast abscess requiring IV antibiotics hospitalized for 2 days, 3) Multiple episodes of emesis, 4) Signs of respiratory distress subcostal & intercostal retractions & grunting, 5) Weight down 15%@readmission, 6) Tachypnea, which resolved within 4 hours. For letrozole these included 1) Renal Pelvicaliectasis, 2) Hospitalized a few days later for acid reflux and inadequate intake. For gonadotropin these included 1) One twin baby had severe kidney dilation and another twin baby had hyperglycemia, 2) Increased reflux.

Table S9. Placental Abnormality

Case number	Treatment group	Brief description of placental abnormality
1	Clomiphene	Placenta with succenturiate lobe
2	Clomiphene	Placental disc infarction
3	Clomiphene	Acute chorioamnionitis and umbilical cord with acute funisitis
4	Clomiphene	Marginal cord insertion
6	Gonadatropin	Calcifications
7	Gonadatropin	Acute chorioamnionitis
8	Gonadatropin	Velamentous cord insertion
9	Gonadatropin	Velamentous cord insertion
10	Gonadatropin	Velamentous cord insertion
11	Gonadatropin	Velamentous cord insertion

Figure S1

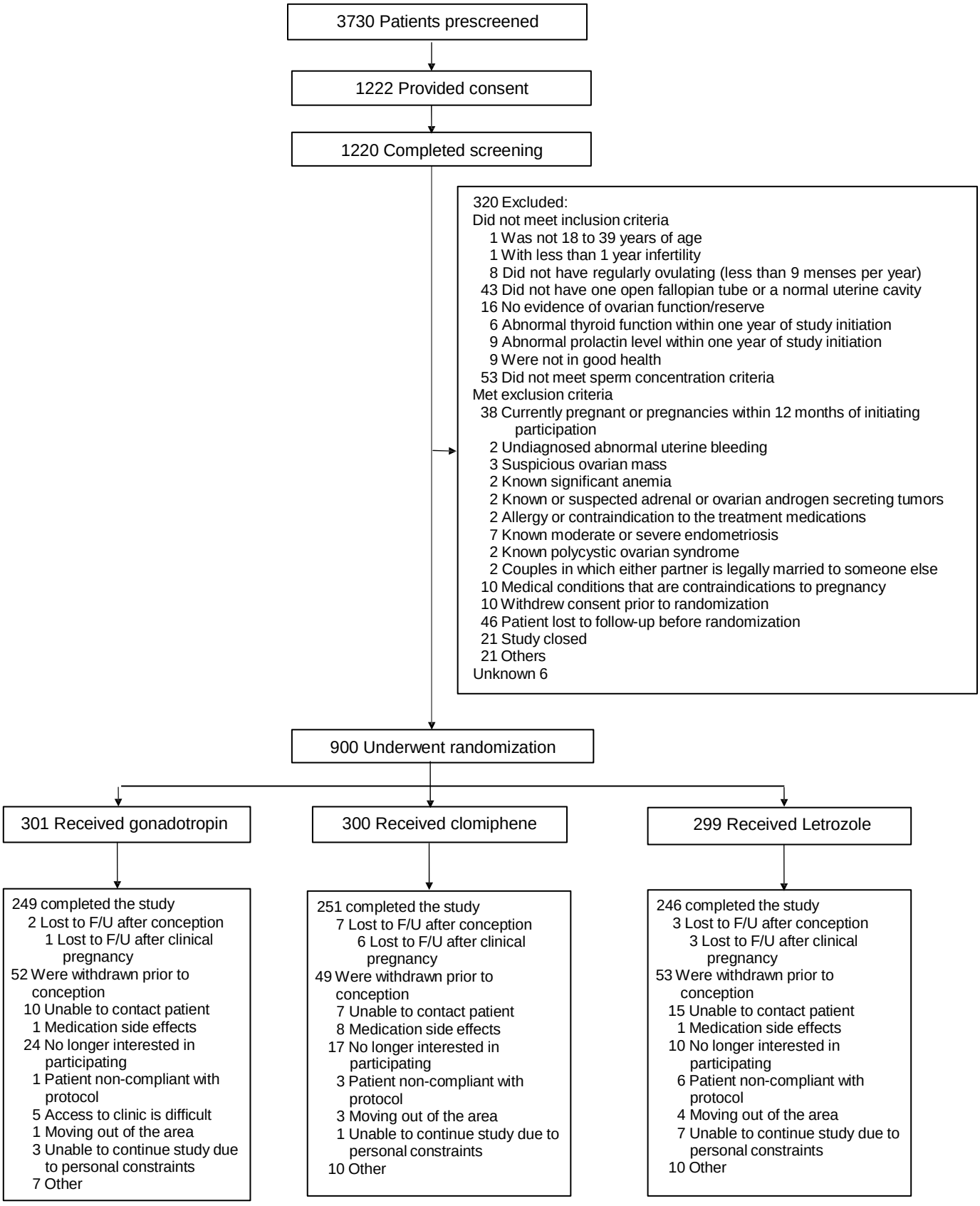

3730 Patients prescreened
1222 Provided consent
1220 Completed screening
320 Excluded:
Did not meet inclusion criteria
1 Was not 18 to 39 years of age
1 With less than 1 year infertility
8 Did not have regularly ovulating (less than 9 menses per year)
43 Did not have one open fallopian tube or a normal uterine cavity
16 No evidence of ovarian function/reserve
6 Abnormal thyroid function within one year of study initiation
9 Abnormal prolactin level within one year of study initiation
9 Were not in good health
53 Did not meet sperm concentration criteria
Met exclusion criteria
38 Currently pregnant or pregnancies within 12 months of initiating participation
2 Undiagnosed abnormal uterine bleeding
3 Suspicious ovarian mass
2 Known significant anemia
2 Known or suspected adrenal or ovarian androgen secreting tumors
2 Allergy or contraindication to the treatment medications
7 Known moderate or severe endometriosis
2 Known polycystic ovarian syndrome
2 Couples in which either partner is legally married to someone else
10 Medical conditions that are contraindications to pregnancy
10 Withdrew consent prior to randomization
46 Patient lost to follow-up before randomization
21 Study closed
21 Others
Unknown 6
900 Underwent randomization
301 Received gonadotropin
300 Received clomiphene
299 Received Letrozole
249 completed the study
2 Lost to F/U after conception
1 Lost to F/U after clinical pregnancy
52 Were withdrawn prior to conception
10 Unable to contact patient
1 Medication side effects
24 No longer interested in participating
1 Patient non-compliant with protocol
5 Access to clinic is difficult
1 Moving out of the area
3 Unable to continue study due to personal constraints
7 Other
251 completed the study
7 Lost to F/U after conception
6 Lost to F/U after clinical pregnancy
49 Were withdrawn prior to conception
7 Unable to contact patient
8 Medication side effects
17 No longer interested in participating
3 Patient non-compliant with protocol
3 Moving out of the area
1 Unable to continue study due to personal constraints
10 Other
246 completed the study
3 Lost to F/U after conception
3 Lost to F/U after clinical pregnancy
53 Were withdrawn prior to conception
15 Unable to contact patient
1 Medication side effects
10 No longer interested in participating
6 Patient non-compliant with protocol
4 Moving out of the area
7 Unable to continue study due to personal constraints
10 Other

Figure S2

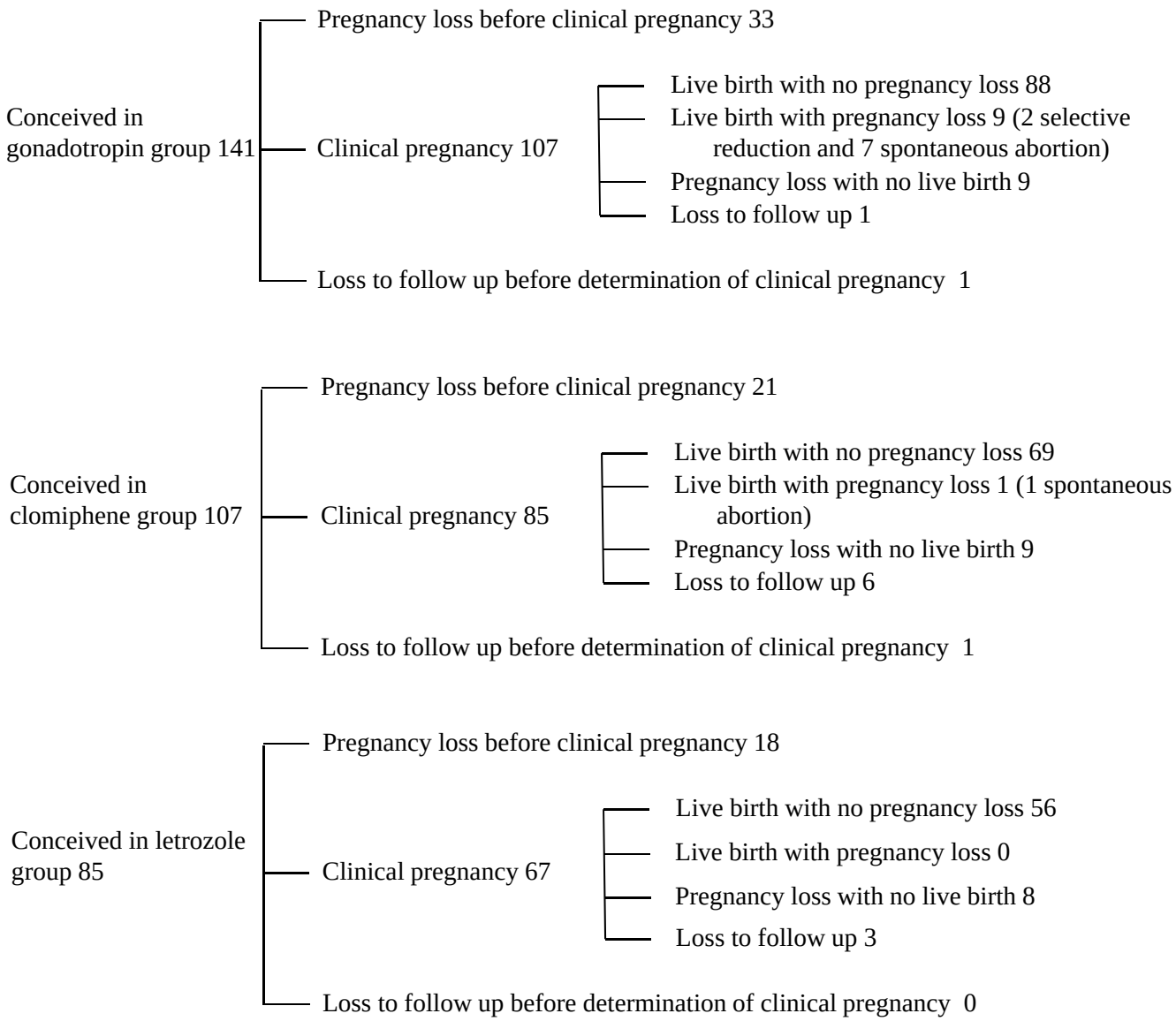

Conceived in gonadotropin group 141
Pregnancy loss before clinical pregnancy 33
Clinical pregnancy 107
Live birth with no pregnancy loss 88
Live birth with pregnancy loss 9 (2 selective reduction and 7 spontaneous abortion)
Pregnancy loss with no live birth 9
Loss to follow up 1
Loss to follow up before determination of clinical pregnancy 1
Conceived in clomiphene group 107
Pregnancy loss before clinical pregnancy 21
Clinical pregnancy 85
Live birth with no pregnancy loss 69
Live birth with pregnancy loss 1 (1 spontaneous abortion)
Pregnancy loss with no live birth 9
Loss to follow up 6
Loss to follow up before determination of clinical pregnancy 1
Conceived in letrozole group 85
Pregnancy loss before clinical pregnancy 18
Clinical pregnancy 67
Live birth with no pregnancy loss 56
Live birth with pregnancy loss 0
Pregnancy loss with no live birth 8
Loss to follow up 3
Loss to follow up before determination of clinical pregnancy 0

Figure S3

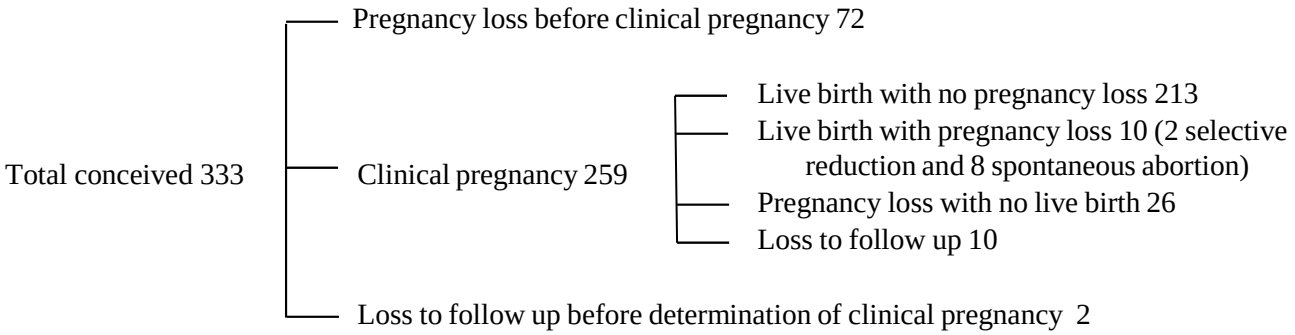
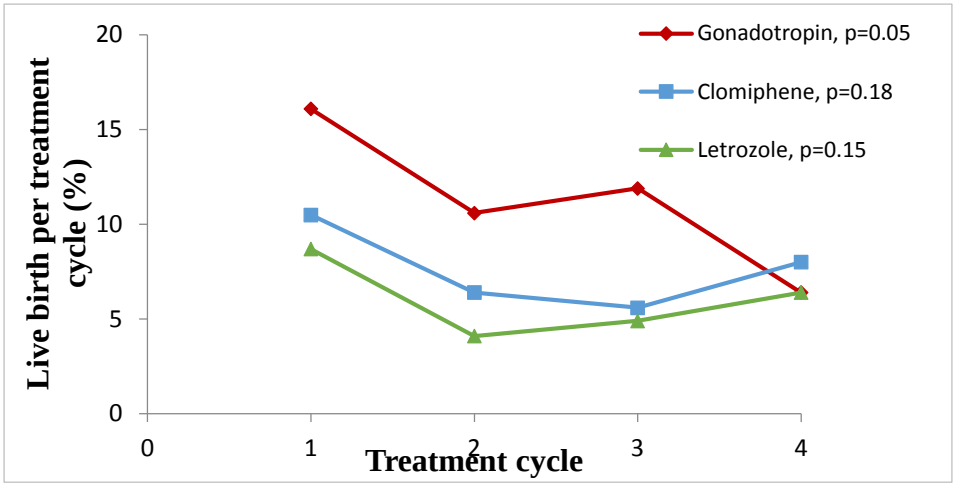
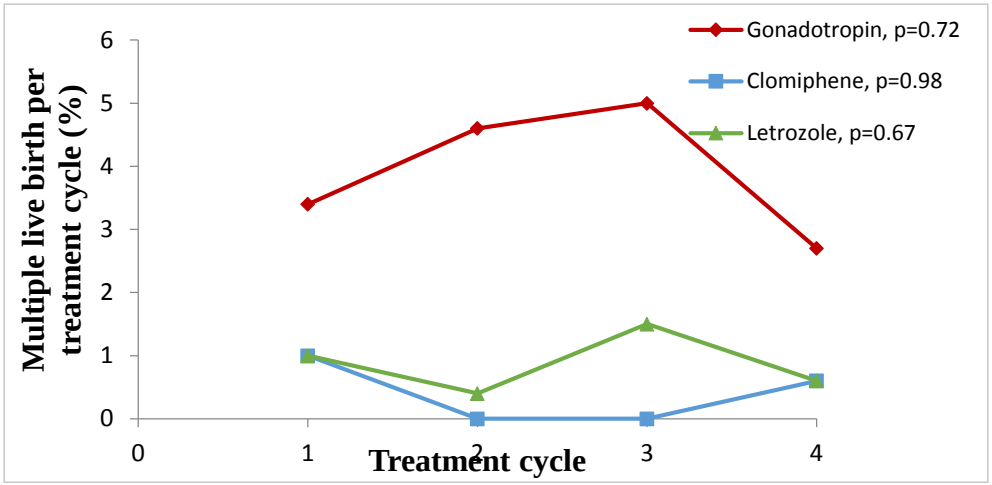
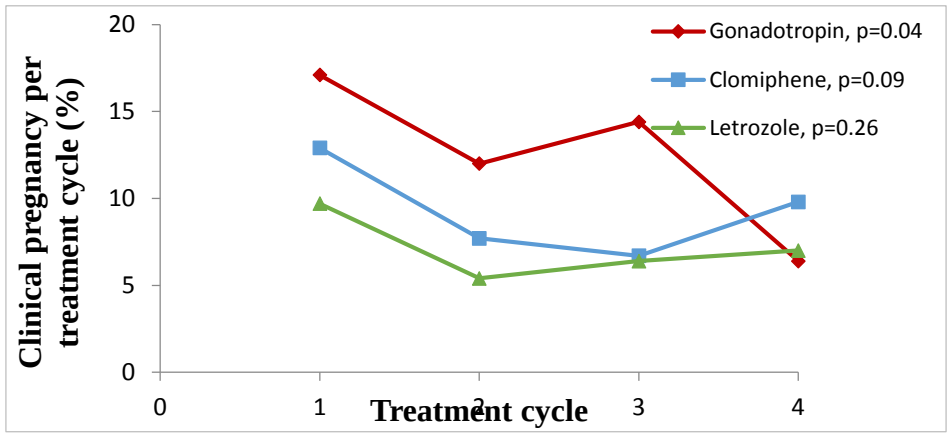
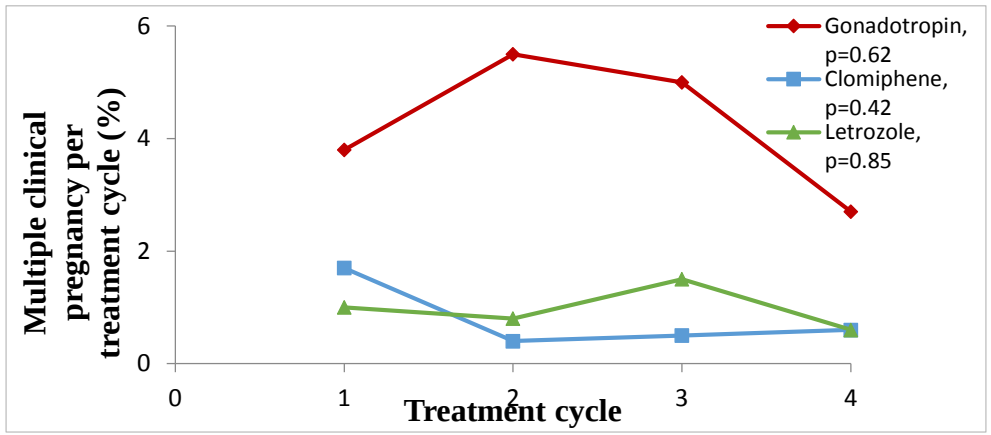

Total conceived 333
Pregnancy loss before clinical pregnancy 72
Clinical pregnancy 259
Live birth with no pregnancy loss 213
Live birth with pregnancy loss 10 (2 selective reduction and 8 spontaneous abortion)
Pregnancy loss with no live birth 26
Loss to follow up 10
Loss to follow up before determination of clinical pregnancy 2

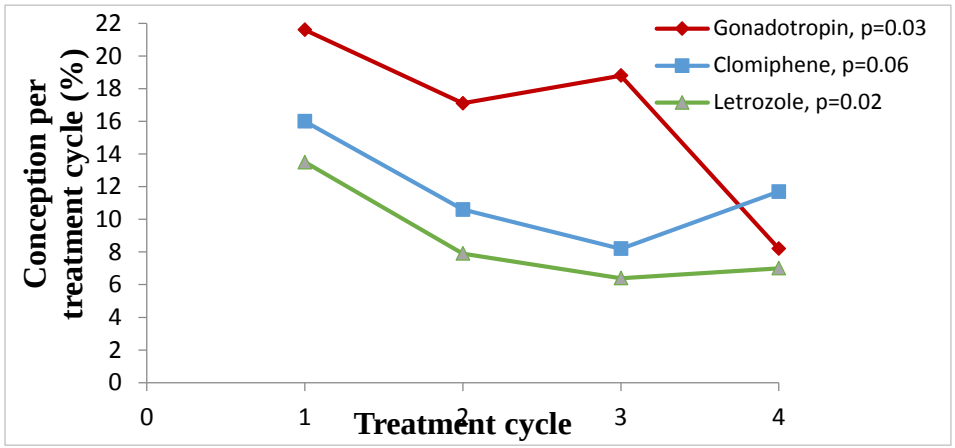
Figure S4. Live birth, multiple live birth, clinical pregnancy, multiple clinical pregnancy, and conception rate per treatment cycle.











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P-value was for the testing of the difference across the 4 treatment cycles